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(54) **PROCESS FOR THE PRODUCTION OF ESTETROL INTERMEDIATES**

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This patent is subject to a terminal disclaimer.

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C07J 51/00 (2006.01)
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(58) **Field of Classification Search**

CPC C07J 1/0018; A61K 31/565; Y02P 20/55
See application file for complete search history.

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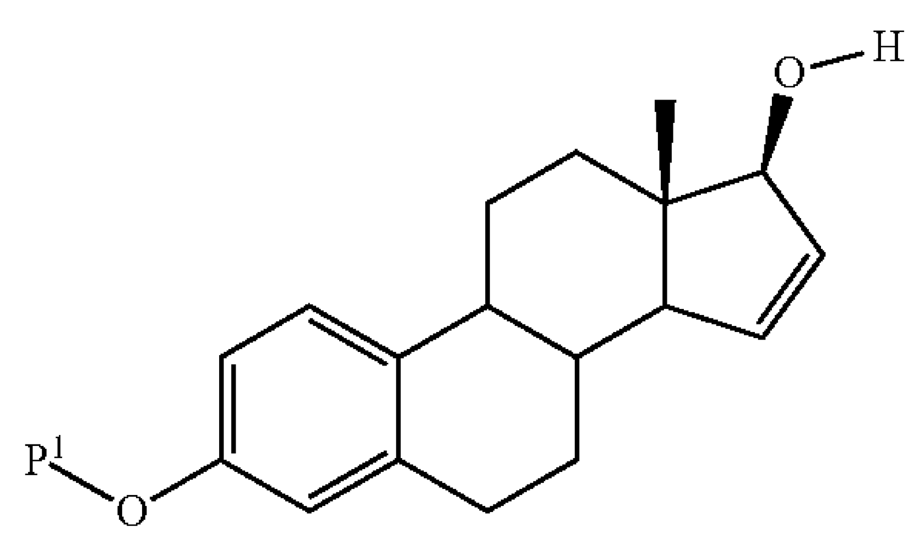
(57) **ABSTRACT**

The present invention relates to a process for the preparation of a compound of formula (I) comprising the steps of a) reacting a compound of formula (II) with a silylating or an acylating agent to produce compound of formula (III), wherein P^1 is a protecting group selected from R^2—Si—R^3R^4 or R^1CO—, R^1 is a group selected from C_{1-6}alkyl or C_{3-6}cycloalkyl, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl; R^2, R^3 and R^4 are each independently a group selected from C_{1-6}alkyl or phenyl, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl; b) halogenation or sulfinylation of the compound of formula (III) to produce a compound of formula (IV); wherein X is halo, or —O—SO—R^5, and R^5 is a group selected from C_{6-10}aryl or heteroaryl, each group being optionally substituted by one or more substituents independently selected from chloro or C_{1-4}alkyl; c) dehalogenation or desulfinylation of the compound of formula (IV) to produce compound of formula (V); and d) reacting the compound of formula (V) with a reducing agent to produce compound of formula (I).

(I)



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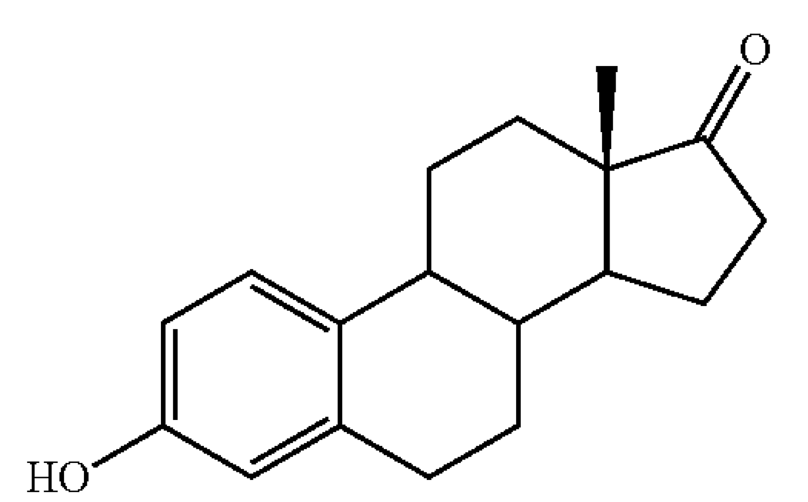

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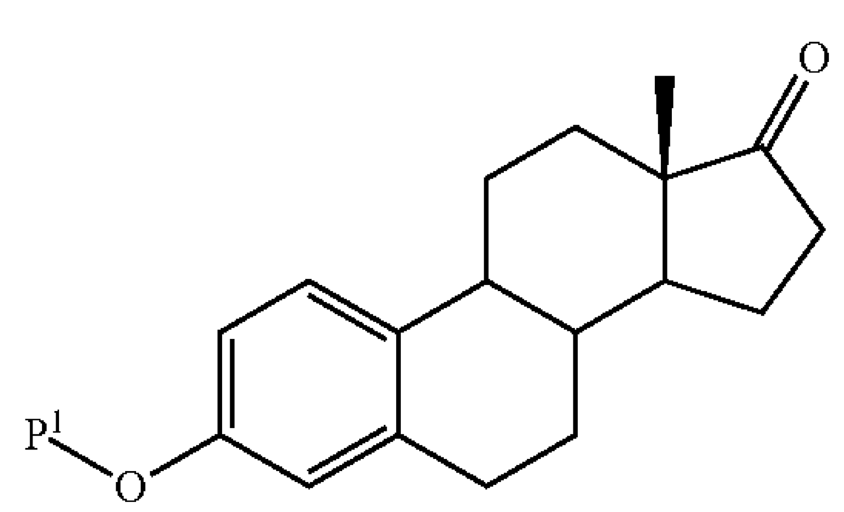

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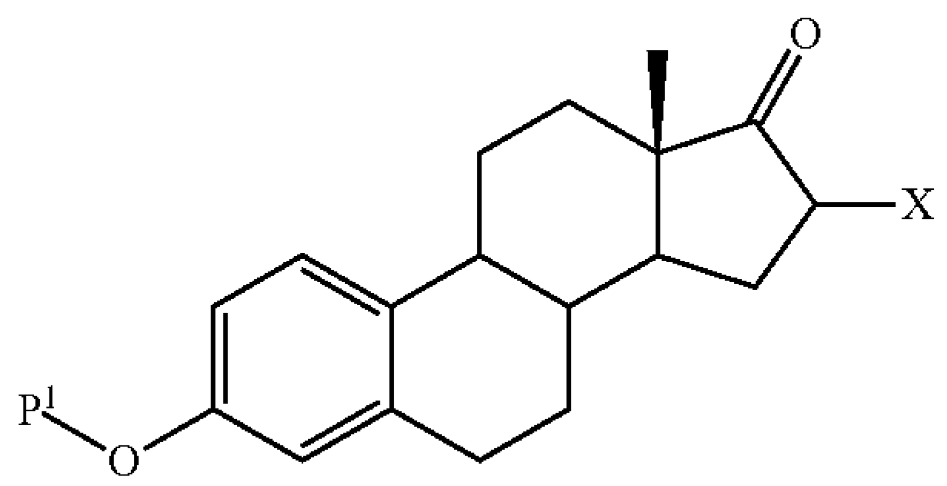

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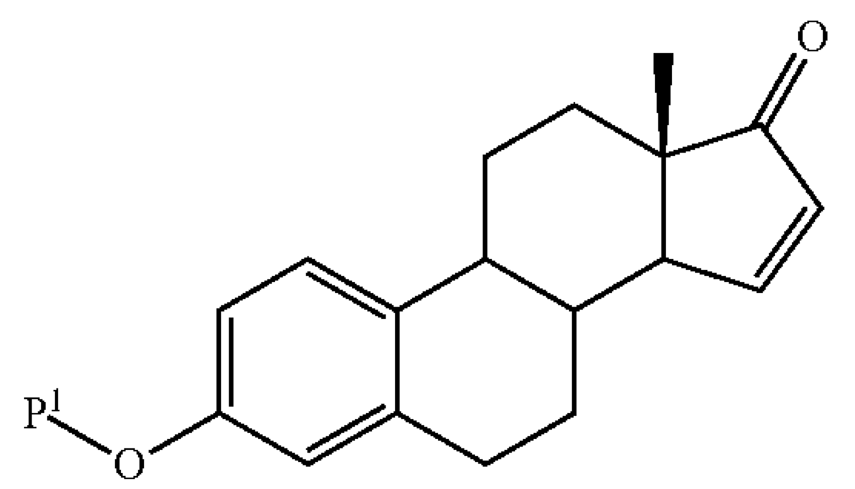

19 Claims, No Drawings

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PROCESS FOR THE PRODUCTION OF ESTETROL INTERMEDIATES

RELATED APPLICATIONS

This application is a 35 U.S.C. § 371 filing of International Application No. PCT/EP2012/060446, filed Jun. 1, 2012; which claims priority to European Patent Application No. 11168560.8, filed on Jun. 1, 2011 and U.S. Provisional Patent Application No. 61/492,297, filed on Jun. 1, 2011. The entire contents of each are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to a new process for the synthesis of a key intermediate in the synthesis of estetrol.

BACKGROUND OF THE INVENTION

Estrogenic substances are commonly used in methods of Hormone Replacement Therapy (HRT) and methods of female contraception. Estetrol is a biogenic estrogen that is endogenously produced by the fetal liver during human pregnancy. Recently, estetrol has been found effective as an estrogenic substance for use in HRT. Other important applications of estetrol are in the fields of contraception, therapy of auto-immune diseases, prevention and therapy of breast and colon tumors, enhancement of libido, skin care, and wound healing.

The synthesis of estetrol and derivatives thereof is known in the art. Verhaar M. T; et al (WO 2004/041839) describes a process for the preparation of estetrol starting from a 3-A-oxy-estra 1,3,5(10),15-tetraen-17-one, wherein A is a C_1-C_5 alkyl group, or a C_7-C_{12} benzylic group. In this document, 3-A-oxy-estra 1,3,5(10),15-tetraen-17-ol is prepared in 6 steps from estrone where A is a benzyl group, the steps comprising protection of the 3-OH group by a benzyl group, then transformation of the 17-keto-group to a 17,17-ethylenedioxy derivative which is halogenated at the C_{16} position using pyridinium bromide perbromide. Dehydrohalogenation is carried out by using potassium terbutoxyde in dimethylsulfoxide. Deprotection of the 17-keto-group is conducted using p-toluene-sulfonic acid monohydrate in aqueous acetone. Reduction of 17-keto-group affords the 17-ol derivative.

One of the disadvantages of the process described in WO 2004/041839 is the protection of 3-OH function with a benzyl group which can be removed only by hydrogenation using Pd/C as catalyst in the last steps of the estetrol synthesis. Furthermore the level of this catalyst in the final drug substance must be determined and must comply with the ICH guidelines.

Another disadvantage of the synthesis described in WO 2004/041839 is the two step protection/deprotection of the 17-keto function in order to generate the 15-16 double bond with a low yield.

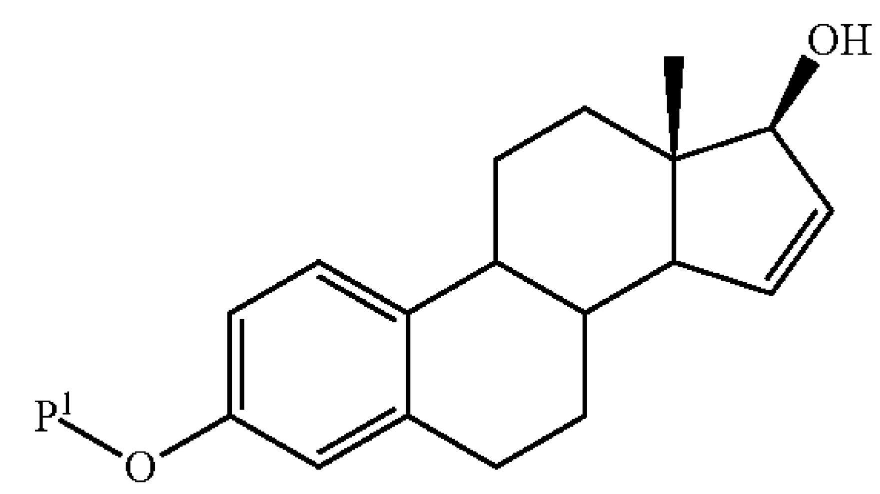
There remain a need for an improved synthesis of 3-Protected-oxy-estra-1,3,5(10),15-tetraene-17-ol. It is therefore an object of the present invention to provide a process for the preparation of 3-Protected-oxy-estra-1,3,5(10),15-tetraene-17-ol which overcome at least one the disadvantages of the prior art.

SUMMARY OF THE INVENTION

The present inventors have now found that this object can be obtained by using a process as defined in the appended claims.

According to a first aspect of the present invention, a process for the preparation of a compound of formula (I) (3-P^1-oxy-estra-1,3,5(10),15-tetraene-17-ol) is provided:

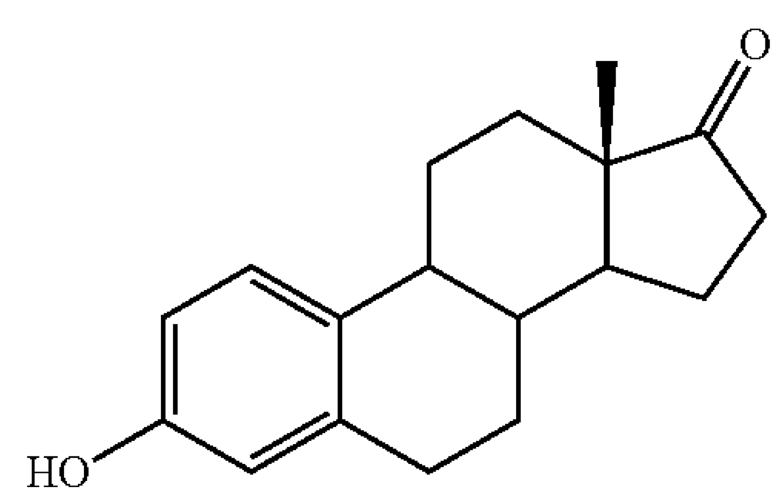
(I)



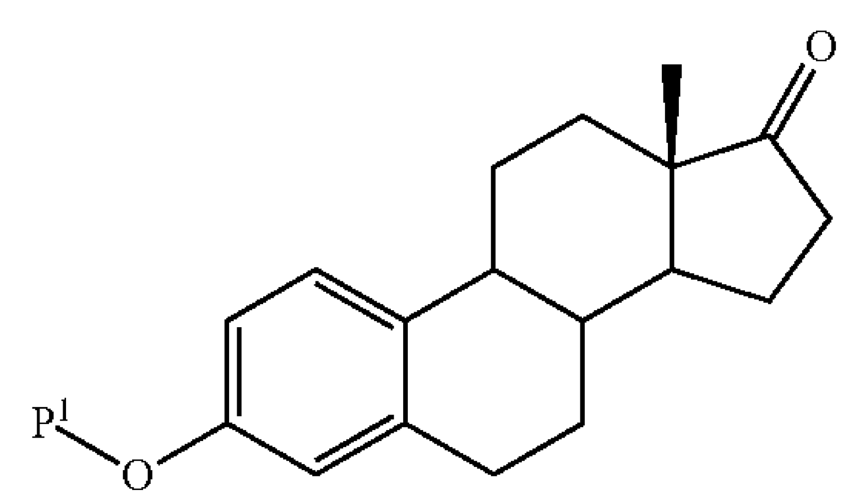
said process comprises the steps of

a) reacting a compound of formula (II) with a silylating or an acylating agent to produce compound of formula (II), wherein P^1 is a protecting group selected from R^2—Si—R^3R^4 or R^1CO—, R^1 is a group selected from C_{1-6}alkyl or C_{3-6}cycloalkyl, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl; R^2, R^3 and R^4 are each independently a group selected from C_{1-6}alkyl or phenyl, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl;

(II)

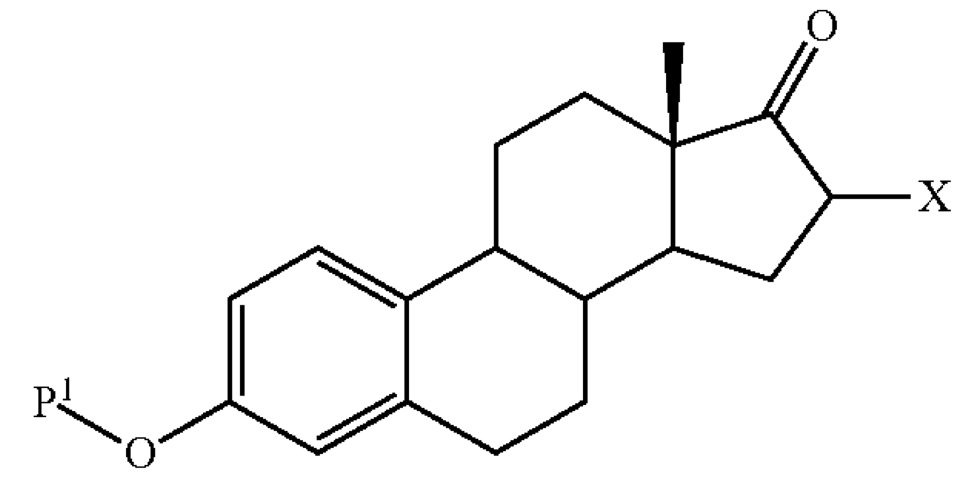


(III)



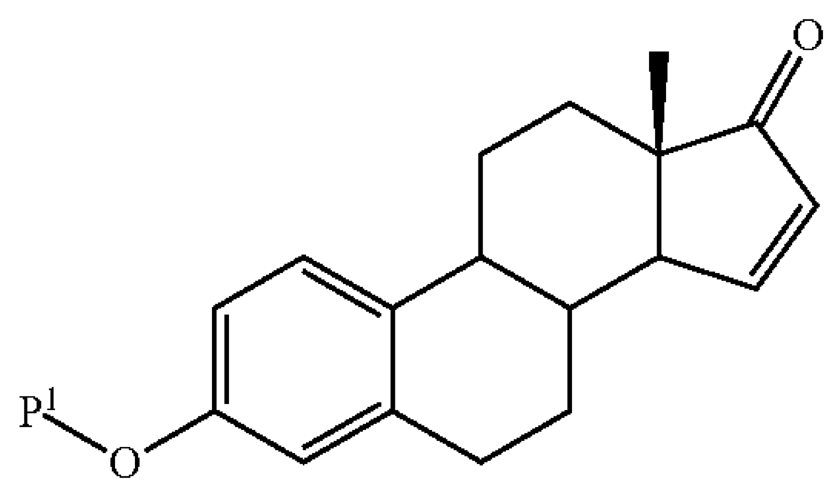
b) halogenation or sulfinylation of the compound of formula (II) to produce a compound of formula (IV); wherein X is halo, or —O—SO—R^5, and R^5 is a group selected from C_{6-10}aryl or heteroaryl, each group being optionally substituted by one or more substituents independently selected from chloro or C_{1-4}alkyl;

(IV)



c) dehalogenation or desulfinylation of the compound of formula (IV) to produce compound of formula (V); and

(V)



d) reacting the compound of formula (V) with a reducing agent to produce compound of formula (I).

The invention provides an improved process for producing 3-P^1-oxy-estra-1,3,5(10),15-tetraene-17-ol of formula (I) in significantly higher yield and for at lower cost than possible by the previous known syntheses.

According to a second aspect, the present invention also encompasses a process for the preparation of estetrol, said process comprising preparing a compound of formula (I) by a process according to the first aspect of the invention and further reacting the compound of formula (I) to produce estetrol.

According to a third aspect, the present invention also encompasses estetrol directly obtained by the process according to the second aspect of the invention, for use in a method selected from a method of hormone replacement therapy, a method of treating vaginal dryness, a method of contraception, a method of enhancing libido, of method of treating skin, a method of promoting wound healing, and a method of treating or preventing a disorder selected from the group consisting of autoimmune diseases, breast tumors and colorectal tumors.

The above and other characteristics, features and advantages of the present invention will become apparent from the following detailed description, which illustrate, by way of example, the principles of the invention.

DETAILED DESCRIPTION OF THE INVENTION

It is to be understood that the terminology used herein is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

As used herein, the singular forms "a", "an", and "the" include both singular and plural referents unless the context clearly dictates otherwise.

The terms "comprising", "comprises" and "comprised of" as used herein are synonymous with "including", "includes" or "containing", "contains", and are inclusive or open-ended and do not exclude additional, non-recited members, elements or method steps. It will be appreciated that the terms "comprising", "comprises" and "comprised of" as used herein comprise the terms "consisting of", "consists" and "consists of".

The recitation of numerical ranges by endpoints includes all numbers and fractions subsumed within the respective ranges, as well as the recited endpoints.

All references cited in the present specification are hereby incorporated by reference in their entirety. In particular, the teachings of all references herein specifically referred to are incorporated by reference.

Unless otherwise defined, all terms used in disclosing the invention, including technical and scientific terms, have the

meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. By means of further guidance, term definitions are included to better appreciate the teaching of the present invention.

In the following passages, different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment, but may. Furthermore, the particular features, structures or characteristics may be combined in any suitable manner, as would be apparent to a person skilled in the art from this disclosure, in one or more embodiments. Furthermore, while some embodiments described herein include some but not other features included in other embodiments, combinations of features of different embodiments are meant to be within the scope of the invention, and form different embodiments, as would be understood by those in the art. For example, in the appended claims, any of the claimed embodiments can be used in any combination.

The term "alkyl" by itself or as part of another substituent, refers to a straight or branched saturated hydrocarbon group joined by single carbon-carbon bonds having 1 to 6 carbon atoms, for example 1 to 5 carbon atoms, for example 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. Thus, for example, C_{1-6}alkyl means an alkyl of one to six carbon atoms. Examples of alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 2-methylbutyl, pentyl iso-amyl and its isomers, hexyl and its isomers.

The term "C_{3-6}cycloalkyl", as a group or part of a group, refers to a saturated cyclic alkyl radical containing from about 3 to about 6 carbon atoms. Examples of monocyclic C_{3-6}cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

The term "C_{2-6}alkenyl" by itself or as part of another substituent, refers to an unsaturated hydrocarbyl group, which may be linear, or branched, comprising one or more carbon-carbon double bonds. Examples of C_{2-6}alkenyl groups are ethenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl and its isomers, 2-hexenyl and its isomers, 2,4-pentadienyl and the like.

The term "C_{6-10}aryl", by itself or as part of another substituent, refers to a polyunsaturated, aromatic hydrocarbyl group having a single ring (i.e. phenyl) or multiple aromatic rings fused together (e.g. naphthyl). or linked covalently, typically containing from 6 to 10 carbon atoms, wherein at least one ring is aromatic. C_{6-10}aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated herein. Non-limiting examples of C_{6-10}aryl comprise phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydro-naphthyl.

The term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo, or iodo.

The term "C_{6-10}arylC_{1-6}alkyl", by itself or as part of another substituent, refers to a C_{1-6}alkyl group as defined herein, wherein one or more hydrogen atoms are replaced by one or more C_{6-10}aryl as defined herein. Examples of aralkyl radicals include benzyl, phenethyl, dibenzylmethyl, methylphenylmethyl, 3-(2-naphthyl)-butyl, and the like.

The term "C_{1-6}alkylcarbonyl", as a group or part of a group, represents a group of Formula —CO—R^a, wherein R^a is C_{1-6}alkyl as defined herein.

The term "C_{3-6}cycloalkylcarbonyl", as a group or part of a group, represents a group of Formula —CO—R^c, wherein R^a is C_{3-6}cycloalkyl as defined herein.

The term "C_{2-6}alkenylC_{1-6}alkanoate" refers to a compound having the Formula R^b—O—CO—R^a wherein R^a is C_{1-6}alkyl as defined herein and R^b is C_{2-6}alkenyl as defined herein.

The term "C_{2-6}alkenylC_{3-6}cycloalkanoate" refers to a compound having the Formula R^b—O—CO—R^c wherein R^c is C_{3-6}cycloalkyl as defined herein and R^b is C_{2-6}alkenyl as defined herein.

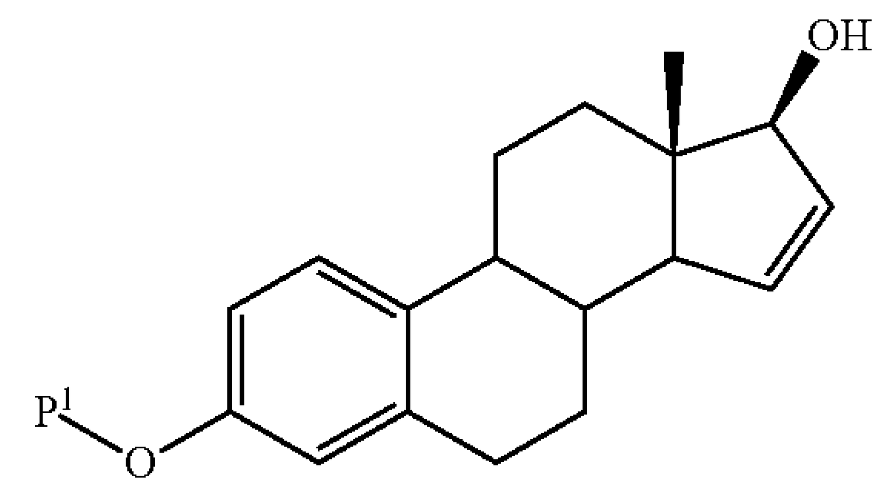
The term "heteroaryl", by itself or as part of another substituent, refers to an aromatic monocyclic or polycyclic heterocycles having preferably 5 to 7 ring atoms and more preferably 5 to 6 ring atoms, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur. Non-limiting examples of a heteroaryl include: pyridinyl, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazinyl, dioxinyl, thiazinyl, triazinyl. Preferably heteroaryl is selected from the group comprising pyridinyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, and pyrazinyl. More preferably heteroaryl is pyridinyl.

The present invention relates to a process for preparing 3-P^1-oxy-estra-1,3,5(10),15-tetraene-17-ol of formula (I), wherein P^1 is a protecting group selected from R^2—Si—R^3R^4; or R^1CO—, wherein

R^1 is a group selected from C_{1-6}alkyl or C_{3-6}cycloalkyl, each group being optionally substituted by 1, 2 or 3 substituents independently selected from fluoro or C_{1-4}alkyl; preferably R^1 is selected from the group comprising methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each group being optionally substituted by 1, 2 or 3 substituents independently selected from fluoro or C_{1-4}alkyl; more preferably R^1 is methyl, ethyl, propyl, isopropyl, cyclopentyl, or cyclohexyl, yet more preferably R^1 is methyl, or ethyl;

R^2, R^3 and R^4 are each independently a group selected from C_{1-6}alkyl or phenyl, said C_{1-6}alkyl or phenyl, being optionally substituted with 1, 2 or 3 substituents independently selected from fluoro or C_{1-6}alkyl; preferably R^2, R^3 and R^4 are each independently selected from the group comprising methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, and phenyl, each group being optionally substituted with 1, 2 or 3 substituents each independently selected from fluoro or C_{1-4}alkyl; preferably R^2, R^3 and R^4 are each independently selected from the group comprising methyl, ethyl, propyl, isopropyl, or tert-butyl, and phenyl, each group being optionally substituted with 1, 2 or 3 substituents each independently selected from fluoro or C_{1-2}alkyl,

(I)

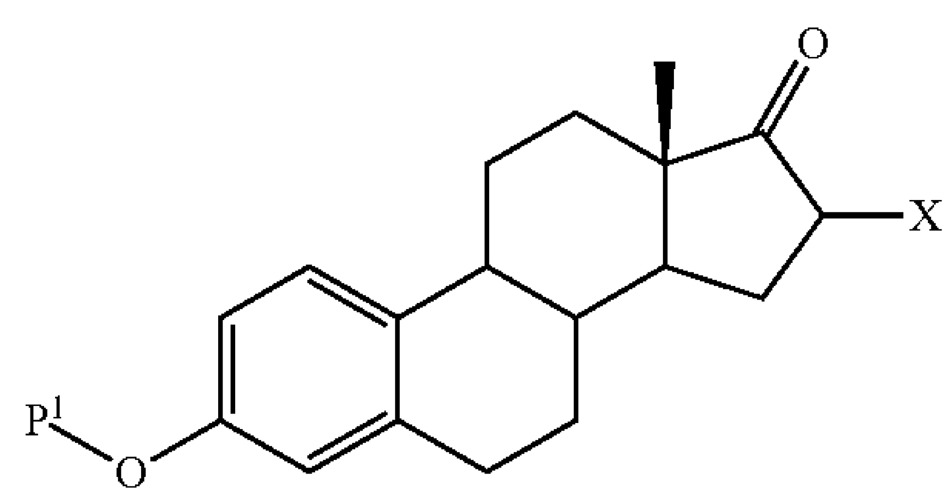


said process comprising the steps of:

a) protecting the hydroxyl of estrone of formula (II) to produce compound of formula (III), wherein P^1 is as defined above,

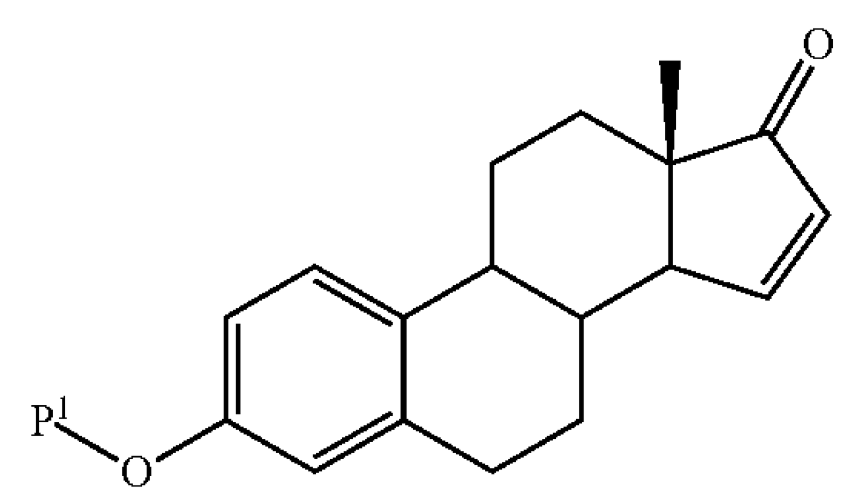
b) halogenation or sulfinylation of the compound of formula (II) to produce a compound of formula (IV); wherein X is halo, or —O—SO—R^5, and R^5 is a group selected from C_{6-10}aryl or heteroaryl, each group being optionally substituted by one or more substituents independently selected from chloro or C_{1-4}alkyl;

(IV)



c) dehalogenation or desulfinylation of the compound of formula (IV) to produce compound of formula (V); and

(V)



d) reacting the compound of formula (V) with a reducing agent to produce compound of formula (I);

and if necessary any protective group used in the reactions described above is cleaved concurrently or subsequently; and

if desired, compound of formula (I) is subsequently converted into another compound by routine processes applicable for conversion of functional groups,

if desired a compound of formula I thus obtained is resolved into its stereoisomers.

In an embodiment, P^1 is R^2—Si—R^3R^4. Preferably P^1 is selected from the group comprising tert-butyl-dimethyl-silyl, diphenyl-methyl-silyl, dimethyl-phenyl-silyl, trimethyl-silyl, triethyl-silyl and triisopropyl-silyl, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl; more preferably P^1 is tert-butyl-dimethyl-silyl.

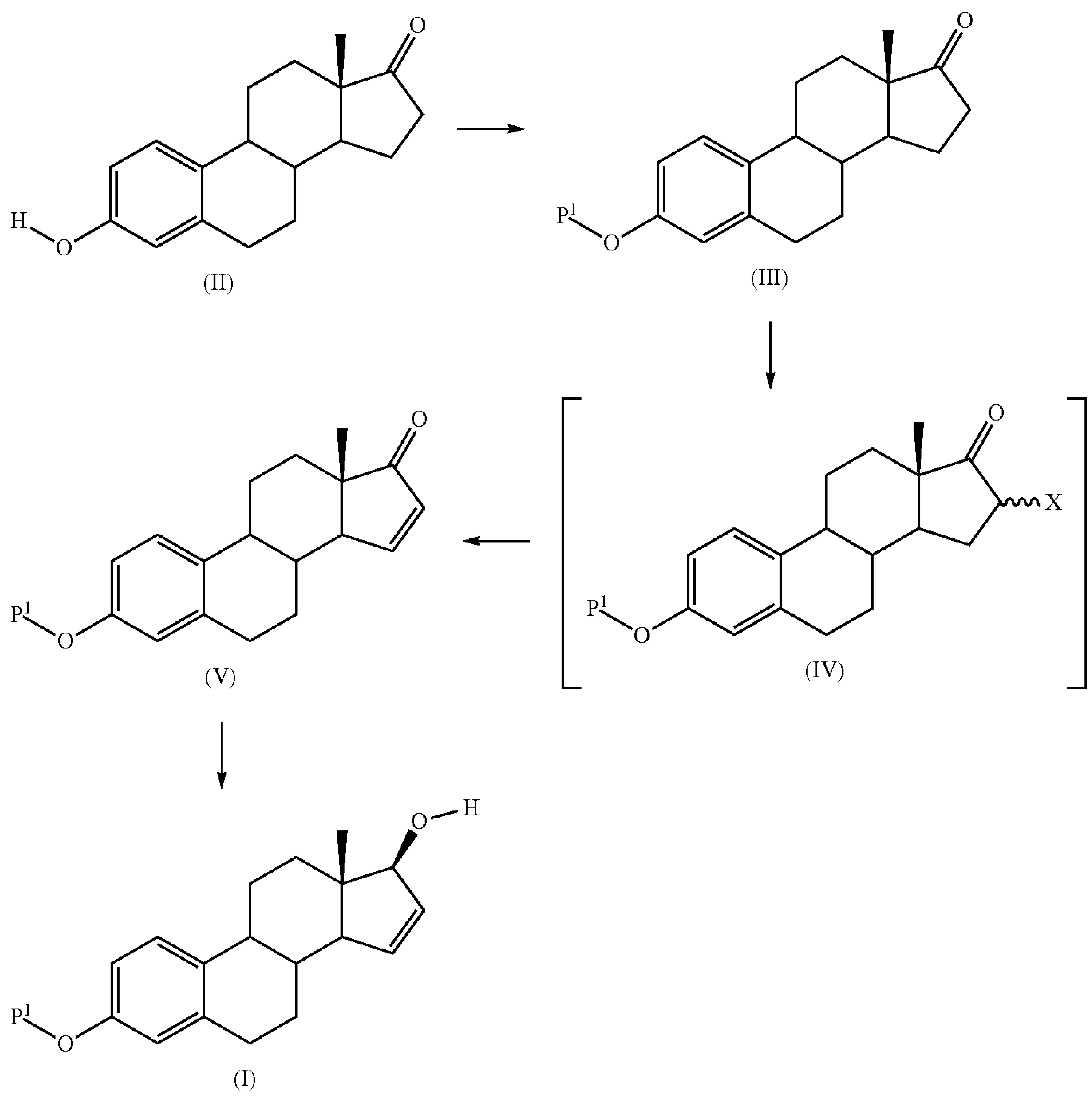
In an embodiment, the silylating agent can be selected from the group comprising C_{1-6}alkylsilylchloride, C_{1-6}alkylsilyltriflate, phenylsilylchloride, phenylsilyltriflate,

C_{1-6}alkyl phenylsilylchloride, C_{1-6}alkylphenylsilyltriflate, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl.

In another embodiment, P^1 is R^1CO—; preferably P^1 is a group selected from C_{1-4}alkylcarbonyl or C_{4-6}cycloalkylcarbonyl, each group being optionally substituted by 1, 2 or 3 substituents independently selected from fluoro or C_{1-4}alkyl; more preferably P^1 is a group selected from C_{1-2}alkylcarbonyl or C_{5-6}cycloalkylcarbonyl, each group being optionally substituted by 1, 2 or 3 substituents independently selected from fluoro or C_{1-2}alkyl; for example P^1 is selected from acetyl, or cyclohexylcarbonyl, preferably P^1 is acetyl.

In an embodiment, the process for the preparation of 3-P^1-estra 1,3,5(10),15-tetraene-17-ol of formula (I) from estrone of formula (II) can be preformed as shown in Scheme 1. The compound of formula (I) can then be further reacted to prepare estetrol.

Scheme 1



According to scheme 1, the hydroxyl of estrone of formula (II) is protected, to produce compound of formula (III).

In an embodiment, estrone of formula (II) is reacted with a silylating agent. The silylating agent can be selected from the group comprising C_{1-6}alkylsilylchloride, C_{1-6}alkylsilyltriflate, phenylsilylchloride, phenylsilyltriflate, C_{1-6}alkylphenylsilyl chloride, C_{1-6}alkylphenylsilyltriflate, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl.

For example, formation of protected estrone silyl ether can be performed by reaction of a silylating agent such as tert-butyl dimethylsilylchloride, diphenylmethylsilylchloride, dimethylphenylsilylchloride, trimethylsilylchloride, triethylsilylchloride, or triisopropylsilylchloride, or such as tert-butyl dimethylsilyltriflate, diphenylmethylsilyltriflate, dimethylphenylsilyltriflate, trimethylsilyltriflate, triethylsilyltriflate, or triisopropylsilyltriflate. The reaction can be performed in the presence of a suitable base such as imidazole, 2,6-lutidine, collidine, triethylamine, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction can be performed at room temperature or under reflux. The reaction can be performed in the presence of a suitable solvent such as dichloromethane, toluene, or dimethylformamide or a mixture thereof.

In another embodiment, estrone of formula (II) is reacted with an acylating agent. In an embodiment, said acylating agent can be selected from the group comprising C_{2-6}alkenylC_{1-6}alkanoate, C_{2-6}alkenylC_{3-6}cycloalkanoate, acyl chloride, and anhydrides. Preferably, the acylating agent is selected from the group comprising C_{2-6}alkenylpropanoate, C_{2-6}alkenylbutanoate, C_{2-6}alkenylpentanoate, C_{2-6}alkenylhexanoate, C_{2-6}alkenylcyclopropanoate, C_{2-6}alkenylcyclobutanoate, C_{2-6}alkenylcyclopentanoate, and C_{2-6}alkenylcyclohexanoate, acyl chloride and anhydrides. More preferably, the acylating agent is selected from the group comprising isopropenyl acetate, isopropenyl propionate, isopropenyl butyrate, isopropenyl isobutyrate, vinyl acetate, vinyl propionate, prop-2-enyl cyclohexanecarboxylate, ethenyl cyclopentanecarboxylate, vinyl cyclohexanoate, acetyl chloride, propionylchloride, butyrylchloride, acetic anhydride and the like. More preferably, the acylating agent is selected from the group comprising isopropenyl acetate, isopropenyl propionate, isopropenyl butyrate, isopropenyl isobutyrate, vinyl acetate, vinyl propionate, acetyl chloride, propionylchloride, butyrylchloride, acetic anhydride and the like.

The acylation when performed with C_{2-6}alkenylC_{1-6}alkanoate or C_{2-6}alkenylC_{3-6}cycloalkanoate, can be performed in the presence of an acid, such as in the presence of sulfuric acid, or in the presence of a C_{6-10}arylsulfonic acid, optionally substituted by one or more chloro substituents. Non-limiting examples of a suitable acid include para-toluene sulfonic acid, and sulfuric acid.

The acylation when performed with an acyl chloride or an anhydride, can be performed in the presence of an organic base, such as imidazole, triethylamine and the like.

Step (b) of the process comprises halogenation or sulfinylation of the compound of formula (III) to produce a compound of formula (IV); wherein X is halo, or —O—SO—R^5, and R^5 is a group selected from C_{6-10}aryl or heteroaryl, each group being optionally substituted by one or more substituents independently selected from chloro or C_{1-4}alkyl; preferably R^5 is phenyl or pyridinyl.

In an embodiment, step (b) is a halogenation and the halogenation is performed by reacting the compound of formula (III) with a halogenating reagent.

Preferably, step b) is a bromination, and X is bromo. In an embodiment, the brominating reagent can be selected from the group comprising copper(II) bromide, bromine, pyridine bromine perbromine and the like.

In another embodiment, step (b) is a sulfinylation and the sulfinylation is performed by reacting the compound of formula (III) with a base and with a sulfinylation reagent.

Non-limiting examples of sulfinylation reagent include methyl 2-pyridinesulfinate, methyl benzenesulfinate, methyl 4-methyl-benzenesulfinate, and methyl 4-chloro-benzene sulfinate.

The base used in the sulfinylation step can be selected from the group comprising potassium hydride, potassium terbutylate, sodium hydride, sodium terbutylate and a mixture thereof.

Non-limiting examples of suitable experimental conditions for the sulfinylation are described in Barry M Trost et al in Journal of Organic Chemistry, 1993, 58, 1579-81; hereby incorporated by reference.

The next step comprises the dehalogenation or desulfinylation of the compound of formula (IV) to produce compound of formula (V).

In an embodiment, step (c) is a halogenation, and step (d) comprises a dehalogenation step which can be performed in the presence of a base. The base can be selected from the group comprising imidazole, collidine, 2,6-lutidine, triethylamine, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The dehalogenation reaction can be performed at a temperature between 30° C. and 130° C. Preferably, the dehalogenation reaction is performed in an aprotic solvent.

In another embodiment, step (c) is a sulfinylation, and step (d) comprises a desulfinylation which can be carried out with heat optionally in the presence of cupric sulfate. The temperature of the desulfinylation step can be between 80° C. and 130° C., preferably between 90° C. and 120° C., preferably between 100° C. and 115° C.

The next step in the process comprises the reduction of the compound of formula (V) with a reducing agent to produce compound of formula (I). Preferably, said reducing agent is a metal hydride compound. For example, the metal hydride compound can be selected from the group comprising

$LiAlH_4$, $NaBH_4$, $NaBH(OAc)_3$, $ZnBH_4$, and $NaBH_4/CeCl_3$. preferably, said reducing agent is $NaBH_4/CeCl_3$.

For example said reduction can be performed in a suitable solvent or a mixture thereof, such as in tetrahydrofuran, or a mixture of methanol and tetrahydrofuran. The reaction can be performed at low temperatures such as below 15° C., for example below 10° C.

The present inventors have surprisingly found that the compound of formula (I) and its intermediates, could be obtained in good yield and improved purity.

The present process has the advantage that 3-P^1-oxy-estra1,3,5(10),15-tetraen-17-ol of formula (I), and subsequently estetrol, can be obtained from estrone with improve yield compared to prior art processes, which is more convenient for an economical and industrial synthesis.

The present invention also encompasses a process for the preparation of estetrol, said process comprising preparing a compound of formula (I) using the process of the invention and further reacting compound of formula (I) to produce estetrol.

The present invention also encompasses the use of estetrol directly obtained by the process the invention for the manufacture of a pharmaceutical composition, preferably for use in a method selected from a method of hormone replacement therapy, a method of treating vaginal dryness, a method of contraception, a method of enhancing libido, of method of treating skin, a method of promoting wound healing, and a method of treating or preventing a disorder selected from the group consisting of autoimmune diseases, breast tumors and colorectal tumors.

The invention is illustrated but not limited by the following examples.

EXAMPLES

Example 1: Preparation of a Compound of Formula (I) wherein P^1 is tert-butyldimethylsilyl According to an Embodiment of the Invention

Step 1: 3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-triene-17-one

To a solution of 3-hydroxy-estra-1,3,5(10)-triene-17-one (100 g, 0.370 mole) in 500 ml of dichloromethane was added tert-butyldimethylsilyl-chloride (58.3 g, 0.388 mole) and imidazole (26.4 g, 0.388 mole). The mixture was stirred for 24 hours at room temperature. Water (300 ml) was added and the organic layer was washed with 200 ml of water. After concentration the product was crystallized from a mixture of ethanol/diisopropyl ether, collected by filtration and dried. It weighted 145 g (95% yield).

^{1}HNMR ($CDCl_3$) δ 0.20 (s, 6H, $(CH_3)_2$—Si—), 0.90 (s, 3H, CH_3 at C-18), 1.00 (s, 9H, $(CH_3)_3$—C—Si—), 1.20-2.60 (m, 13H), 2.75-2.95 (m, 2H), 5.65-5.75 (m, 1H), 6.58 (broad s, 1H, H4), 6.63 (dd, 1H, H2), 7.12 (d, 1H, H1) mp: 171.6° C.

Step 2: 3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-15-tetraene-17-one

A solution of potassium terbutylate (50 g, 0.45 mole) in 800 ml of tetrahydrofuran was treated with 3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-triene-17-one (86.5 g, 0.225 mole) under nitrogen and stirred for 1 hour, then methyl benzenesulfinate (70.2 g, 0.45 mole) and triethylamine were added. After stirring for 2 hours the solution was poured in 1000 ml of water and 70 ml of hydrochloric acid keeping the temperature below 5° C. 1000 ml of toluene was added, phases are separated and the solution was heated to distill off the solvent until the temperature reached 115° C. Reflux was maintained for 5 hours.

Toluene was washed with two time water, and then partially concentrated. Heptane was added. After one hour at 5° C. the solid was collected by filtration and used in the reduction step without further purification.

^{1}HNMR ($CDCl_3$) δ 0.20 (s, 6H, $(CH_3)_2$—Si—), 1.00 (s, 9H, $(CH_3)_3$—C—Si—), 1.13 (s, 3H, CH_3 at C-18), 1.20-2.70 (m, 11H), 2.80-3.00 (m, 2H), 6.10 (dd, 1H, H15), 6.58 (broad s, 1H, H4), 6.62 (dd, 1H, H2), 7.11 (d, 1H, H1), 7.63 (dd, 1H, H16), mp: 165° C.

Step 3: 3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-15-tetraene-17-ol

The material collected in step 2 was dissolved in THF 300 ml and a solution of cerium chloride heptahydrate (123 g, 0.33 mole) in methanol (300 ml) was added. The mixture was cooled to 0° C. and sodium borohybride (17.8 g, 0.47 mole, 1.5 q) was added portionwise keeping the temperature below 9° C. At this end of the addition the mixture was stirred for one hour then quenched by addition of a 2N HCl solution (100 ml), extracted with ethyl acetate and washed with water. The organic layer was partly evaporated then diisopropylether was added. The precipitate was collected by filtration and dried. After crystallization form a mixture of ethanol/diisopropyl ether the title compound was isolated in 90% yield as an off white solid.

^{1}HNMR ($CDCl_3$) δ 0.20 (s, 6H, $(CH_3)_2$—Si—), 0.89 (s, 3H, CH_3 at C-18), 1.00 (s, 9H, $(CH_3)_3$—C—Si—), 1.20-2.40 (m, 10H), 2.75-2.95 (m, 2H), 4.40 (broad s, 1H, H17), 5.65-5.75 (m, 1H), 5.95-6.10 (m, 1H), 6.57 (broad s, 1H, H4), 6.60 (dd, 1H, H2), 7.13 (d, 1H, H1) mp: 107.5° C.

Example 2: Preparation of a Compound of Formula (I) wherein P[1] is tert-butyldimethylsilyl According to an Embodiment of the Invention

Step 1: 3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-triene-17-one

3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-triene-17-one was prepared as described in step 1 of Example 1.

Step 2: 3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-15-tetraene-17-one (via X=Br)

Copper(II) bromide (100 g, 0.45 mole) was added to a warm solution of 3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-triene-17-one (86.4 g, 0.225 mole) in methanol (500 ml) and the mixture was heated under reflux for 2 hours. The hot mixture was filtered and was poured in a mixture of dichloromethane (1000 ml) and water (800 ml). The organic layer was washed with water.

To this solution imidazole (18.3 g, 0.27 mole) was added and heated under reflux for 6 hours. After cooling water (500 ml) was added and the organic layer was concentrated. The residue was crystallized from a mixture of ethyl acetate and heptane.

^{1}HNMR ($CDCl_3$) δ 0.20 (s, 6H, $(CH_3)_2$—Si—), 1.00 (s, 9H, $(CH_3)_3$—C—Si—), 1.13 (s, 3H, CH_3 at C-18), 1.20-2.70 (m, 11H), 2.80-3.00 (m, 2H), 6.10 (dd, 1H, H15), 6.58 (broad s, 1H, H4), 6.62 (dd, 1H, H2), 7.11 (d, 1H, H1), 7.63 (dd, 1H, H16), mp: 165° C.

Step 3: 3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-15-tetraene-17-ol

The reduction step was performed as described in step 3 of example 1: The material collected in step 2 of example 2 was dissolved in THF and a solution of cerium chloride heptahydrate (about 1 eq) in methanol was added. The mixture was cooled to 0° C. and sodium borohybride (1.5 eq) was added portionwise keeping the temperature below 9° C. At this end of the addition the mixture was stirred for one hour then quenched by addition of a 2N HCl solution, extracted with ethyl acetate and washed with water. The organic layer was partly evaporated then diisopropylether was added. The precipitate was collected by filtration and dried. After crystallization form a mixture of ethanol/diisopropyl ether the title compound was isolated as an off white solid.

^{1}HNMR ($CDCl_3$) δ 0.20 (s, 6H, $(CH_3)_2$—Si—), 0.89 (s, 3H, CH_3 at C-18), 1.00 (s, 9H, $(CH_3)_3$—C—Si—), 1.20-2.40 (m, 10H), 2.75-2.95 (m, 2H), 4.40 (broad s, 1H, H17), 5.65-5.75 (m, 1H), 5.95-6.10 (m, 1H), 6.57 (broad s, 1H, H4), 6.60 (dd, 1H, H2), 7.13 (d, 1H, H1) mp: 107.5° C.

Example 3: Preparation of a Compound of Formula (I) wherein P[1] is tert-butyldimethylsilyl According to an Embodiment of the Invention

Step 1: 3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-triene-17-one

3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-triene-17-one was prepared as described in step 1 of Example 1.

Step 2: 3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-15-tetraene-17-one (via X=pyridinesulfinic)

3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-triene 17-one (8.64 g, 0.0225 mole) was added to a suspension of potassium hydride (3 eq. 35% dispersion in oil) in tetrahydrofuran 100 ml. methyl 2-pyridinesulfinate (5.3 g, 0.034 mole, 1.5 eq) was added. After 30 min at room temperature the reaction was poured into a sulfate buffer. The aqueous phase was neutralized by an aqueous solution of sodium carbonate then extracted with toluene. The solution was heated to 110° C. for one hour. After cooling to room temperature the solution was washed with a diluted solution of sodium hydroxide then with water. The organic layer was partly concentrated following by an addition of heptane. The 3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-15-tetraene-17-one was collected by filtration.

^{1}HNMR ($CDCl_3$) δ 0.20 (s, 6H, $(CH_3)_2$—Si—), 1.00 (s, 9H, $(CH_3)_3$—C—Si—), 1.13 (s, 3H, CH_3 at C-18), 1.20-2.70 (m, 11H), 2.80-3.00 (m, 2H), 6.10 (dd, 1H, H15), 6.58 (broad s, 1H, H4), 6.62 (dd, 1H, H2), 7.11 (d, 1H, H1), 7.63 (dd, 1H, H16), mp: 165° C.

Step 3: 3-tert-butyldimethylsilyloxy-estra-1,3,5(10)-15-tetraene-17-ol

The reduction step was performed as described in step 3 of example 1: The material collected in step 2 of example 3 was dissolved in THF and a solution of cerium chloride heptahydrate in methanol was added. The mixture was cooled to 0° C. and sodium borohybride (1.5 eq) was added portionwise keeping the temperature below 9° C. At this end of the addition the mixture was stirred for one hour then quenched by addition of a 2N HCl solution, extracted with ethyl acetate and washed with water. The organic layer was partly evaporated then diisopropylether was added. The precipitate was collected by filtration and dried. After crystallization form a mixture of ethanol/diisopropyl ether the title compound was isolated as an off white solid.

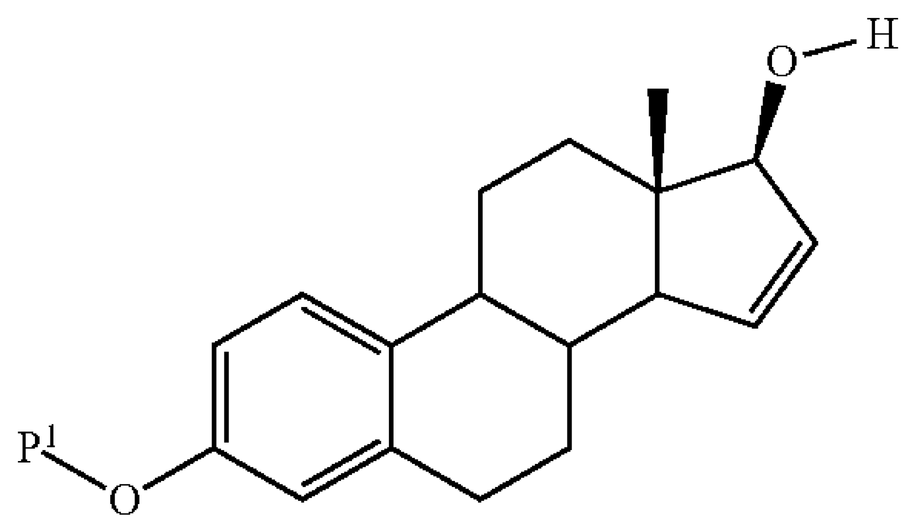
^{1}HNMR ($CDCl_3$) δ 0.20 (s, 6H, $(CH_3)_2$—Si—), 0.89 (s, 3H, CH_3 at C-18), 1.00 (s, 9H, $(CH_3)_3$—C—Si—), 1.20-2.40 (m, 10H), 2.75-2.95 (m, 2H), 4.40 (broad s, 1H, H17), 5.65-5.75 (m, 1H), 5.95-6.10 (m, 1H), 6.57 (broad s, 1H, H4), 6.60 (dd, 1H, H2), 7.13 (d, 1H, H1) mp: 107.5° C.

It is to be understood that although preferred embodiments and/or materials have been discussed for providing embodiments according to the present invention, various modifications or changes may be made without departing from the scope and spirit of this invention.

The invention claimed is:

1. A process for the preparation of a compound of formula (I)

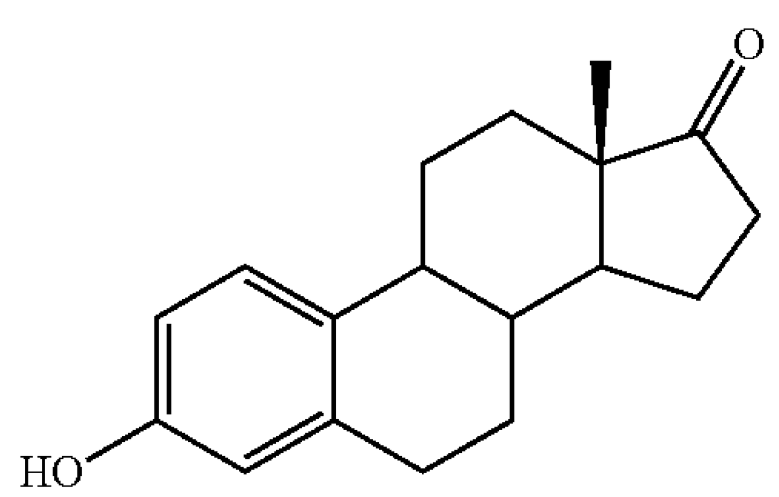
(I)



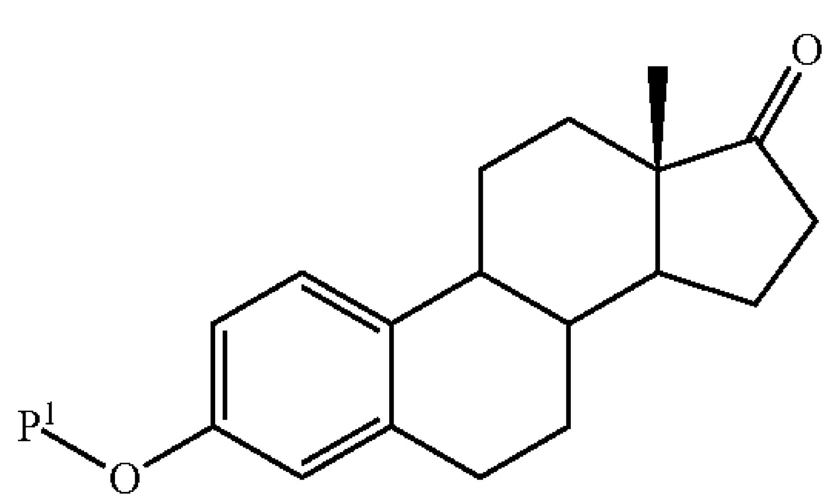
comprising the steps of

a) reacting a compound of formula (II) with a silylating agent to produce a compound of formula (III), wherein P^1 is R^2—Si—R^3R^4; R^2, R^3 and R^4 are each independently a group selected from C_{1-6}alkyl or phenyl, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl;

(II)



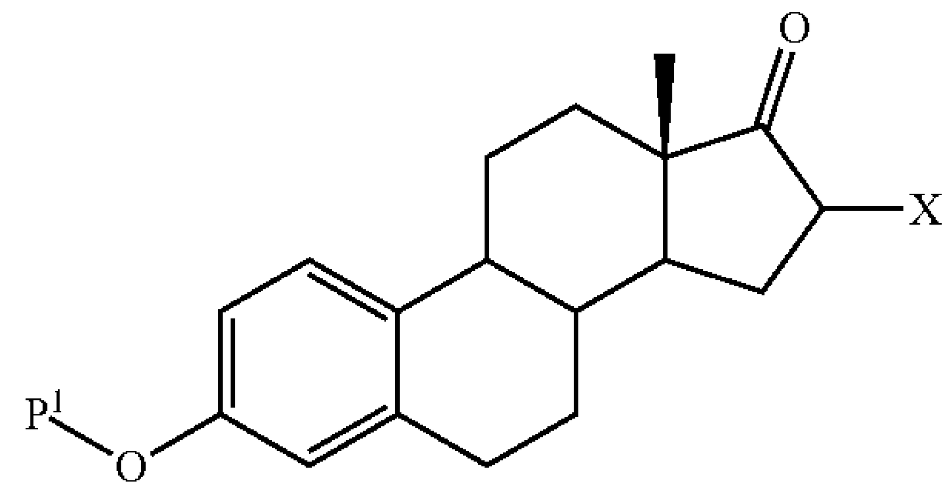
(III)



b) halogenation or sulfinylation of the compound of formula (III) to produce a compound of formula (IV); wherein X is halo, or —SO—R^5, and R^5 is a group selected from C_{6-10}aryl or heteroaryl, each group being optionally substituted by one or more substituents independently selected from chloro or C_{1-4}alkyl;

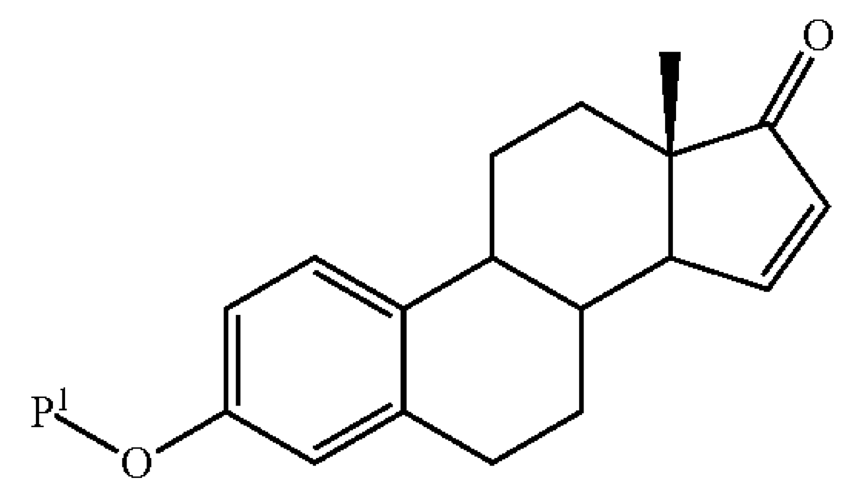
wherein the halogenation or sulfinylation is performed by directly reacting the compound of formula (III) with a halogenation or sulfinylation reagent;

(IV)



c) direct dehalogenation or desulfinylation of the compound of formula (IV) to produce compound of formula (V); and

(V)



d) reacting the compound of formula (V) with a reducing agent to produce compound of formula (I).

2. The process according to claim **1**, wherein step (b) is a sulfinylation and the sulfinylation is performed by reacting the compound of formula (III) with a base and with a sulfinylation reagent.

3. The process according to claim **1** wherein step (b) is a sulfinylation and a sulfinylation reagent is methyl 2-pyridinesulfinate, methyl benzenesulfinate, methyl 4-methylbenzenesulfinate, methyl 4-chloro-benzene sulfinate.

4. The process according to claim **2**, wherein the base used in the sulfinylation step is selected from the group consisting of potassium hydride, potassium terbutylate, sodium hydride, sodium terbutylate and a mixture thereof.

5. The process according to claim **1**, wherein step (b) is a halogenation and the halogenation is performed by reacting the compound of formula (III) with a halogenating reagent.

6. The process according to claim **1** wherein step (b) is a bromination and a brominating reagent is selected from the group consisting of copper(II) bromide, bromine, and pyridinium bromide perbromide.

7. The process according to claim **1**, wherein the desulfinylation step is carried out with heat, or optionally in the presence of cupric sulfate.

8. The process according to claim **1**, wherein the dehalogenation step is performed in the presence of a base.

9. The process according to claim **8**, wherein the base is selected from the group consisting of imidazole, collidine, 2,6-lutidine, triethylamine, or 1,8-diazabicyclo[5.4.0]undec-7-ene.

10. The process according to claim **1**, wherein step (d) is performed using a reducing agent selected from the group consisting of metal hydride compounds.

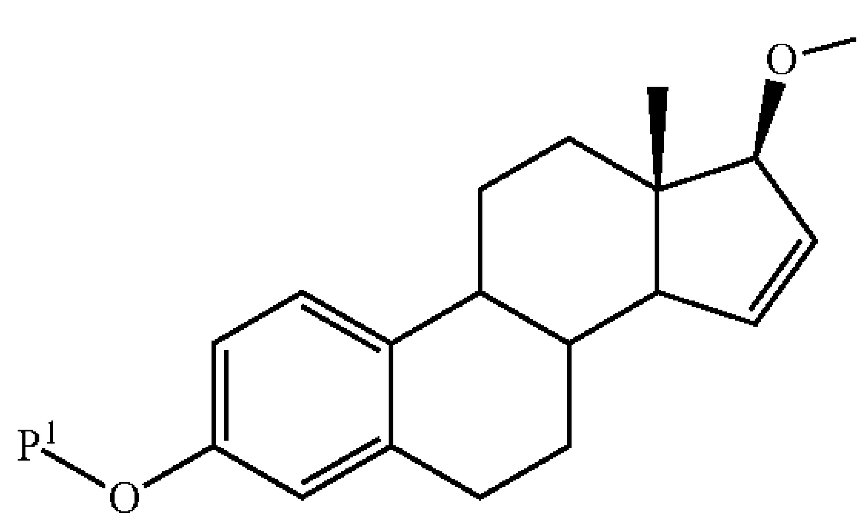
11. The process according to claim **1**, wherein step (d) is performed using a reducing agent selected from the group consisting of $NaBH_4/CeCl_3$, $LiAlH_4$, $NaBH_4$, $NaBH(OAc)_3$, and $ZnBH_4$.

12. The process according to claim **1**, wherein the silylating agent is selected from the group consisting of C_{1-6}alkylsilylchloride, C_{1-6}alkylsilyltriflate, phenylsilylchloride, phenylsilyltriflate, C_{1-6}alkylphenylsilylchloride, C_{1-6}alkylphenylsilyltriflate, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl.

13. The process according to claim **1**, wherein the acylating agent is selected from the group consisting of C_{2-6}alkenylC_{1-6}alkanoates, C_{2-6}alkenylC_{3-6}cycloalkanoates, acyl chlorides and anhydrides.

14. A process for the preparation of estetrol, said process comprising preparing a compound of formula (I) by a process,

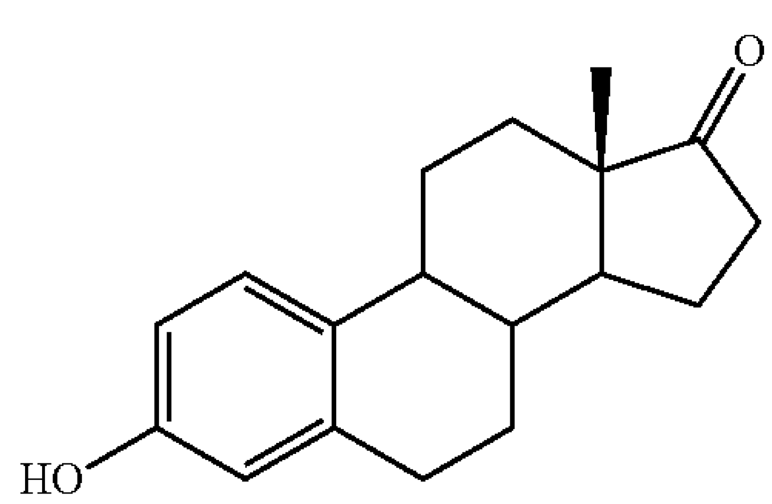
(I)



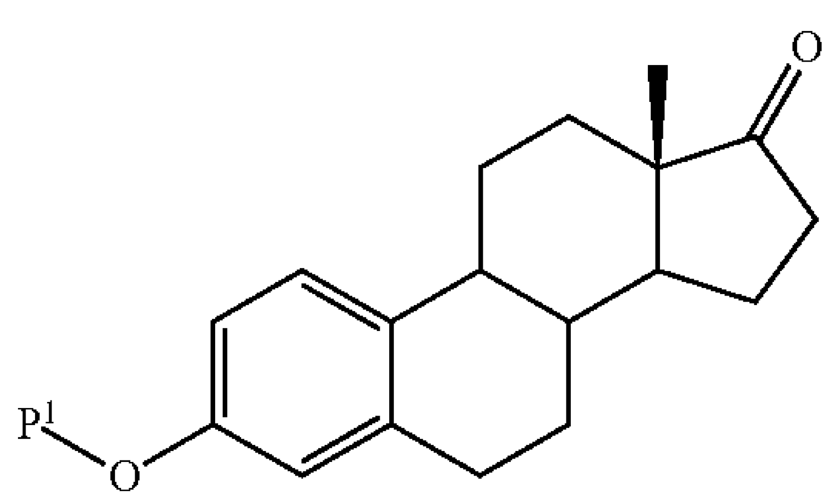
the process comprising the steps of:

a) reacting a compound of formula (II) with a silylating agent to produce a compound of formula (III), wherein P^1 is R^2—Si—R^3R^4; R^2, R^3 and R^4 are each independently a group selected from C_{1-6}alkyl or phenyl, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl;

(II)



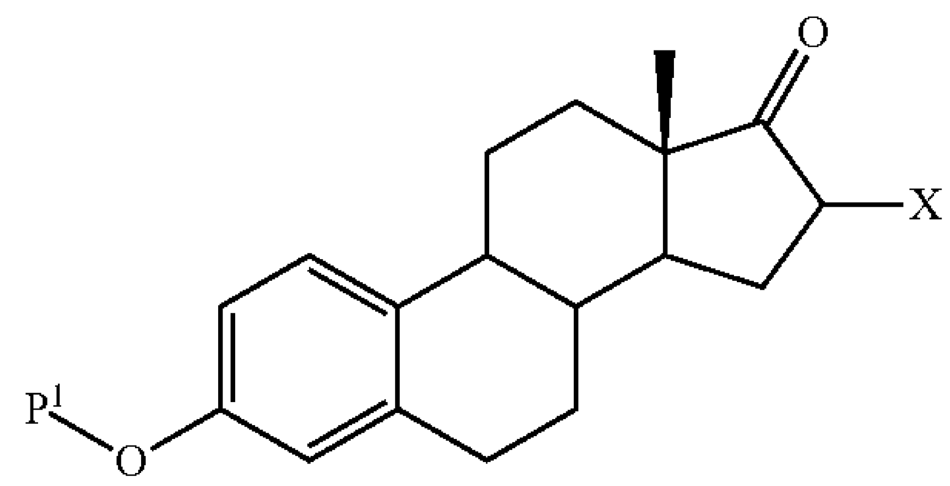
(III)



b) halogenation or sulfinylation of the compound of formula (III) to produce a compound of formula (IV); wherein X is halo, or —SO—R^5, and R^5 is a group selected from C_{6-10}aryl or heteroaryl, each group being optionally substituted by one or more substituents independently selected from chloro or C_{1-4}alkyl;

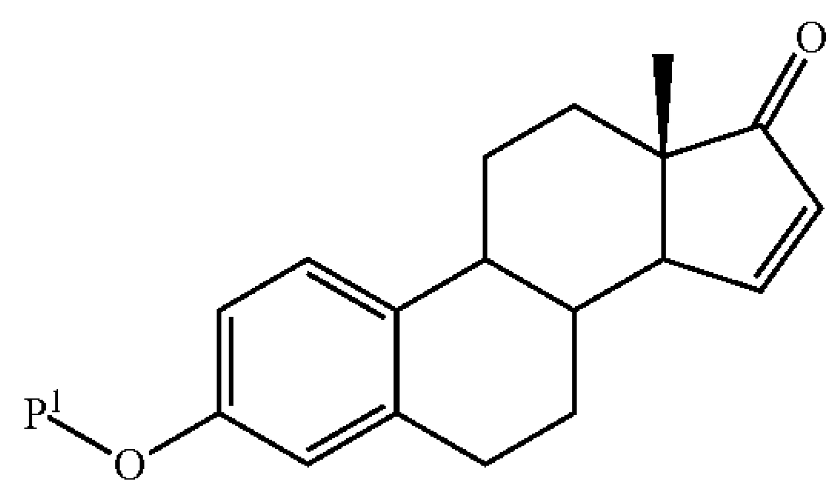
wherein the halogenation or sulfinylation is performed by directly reacting the compound of formula (III) with an halogenation or sulfinylation reagent;

(IV)



c) direct dehalogenation or desulfinylation of the compound of formula (IV) to produce compound of formula (V); and

(V)



d) reacting the compound of formula (V) with a reducing agent to produce compound of formula (I);

and further reacting compound of formula (I) to produce estetrol.

15. The process according to claim **14**, wherein step (b) is a sulfinylation and the sulfinylation is performed by reacting the compound of formula (III) with a base and with a sulfinylation reagent.

16. The process according to claim **14** wherein step (b) is a sulfinylation and a sulfinylation reagent is methyl 2-pyridinesulfinate, methyl benzenesulfinate, 4-methyl-benzenesulfinate, methyl 4-chloro-benzene sulfinate.

17. The process according to claim **15**, wherein the base used in the sulfinylation step is selected from the group consisting of potassium hydride, potassium terbutylate, sodium hydride, sodium terbutylate and a mixture thereof.

18. The process according to claim **14**, wherein step (b) is a halogenation and the halogenation is performed by reacting the compound of formula (III) with a halogenating reagent.

19. The process according to claim **14** wherein step (b) is a bromination and a brominating reagent is selected from the group consisting of copper(II) bromide, bromine, and pyridinium bromide perbromide.

* * * * *